T_3 is also directly secreted by thyroid. On average, the amount of T_4 produced in an adult being of 70 Kg weight every day amounts to 100 μg, while the total production of T_3 amounts to around 25 μg. 4-8 μg of T_3 out of said 25 μg are directly secreted by thyroid and the remaining ones derive from the peripheral conversion of T_4.

T_3 undergoes two different metabolic pathways. The main metabolic pathway consists in the partial deiodination of the inner aromatic ring by type III 5-iodothyronine monodeiodinase (**type III MD**) to give 3,3'-diiodothyronine, which is biologically non-active and is further metabolized through deiodination or sulfoconjugation. The other metabolic pathway regards around 20% of the total amount of T_3 produced by the body and brings on sulfoconjugation of T_3 to give T_3S, which is not able to bond to the thyroid hormones (Ref.2), thus resulting biologically non-active (Ref.3).

Contrary to what happens with T_3, T_3S is not deiodinated by **type III MD**. Rather, it resulted to be an excellent substrate for **type I MD** (Ref.4), which converts it very quickly into 3,3'-diiodothyronine sulphate. On consequence it has been widespread common knowledge that, in the healthy adult being, sulfoconjugation of T_3 to give T_3S represents a way for speeding up the catabolism of T_3, so facilitating its biliary and urinary excretion. Actually, it was found that serum levels of T_3S, physiologically low in the health adult, are higher when **type I MD** activity is reduced.

Yet, it has also unexpectedly been found that, just in some body districts and organs, sulfatases exist which, under particular physiological conditions and situations, are able to convert again T_3S into its active form T_3 (Ref's.7-9).

Such enzymes have been described in the intestinal microflora as well

as in body tissues like liver, kidneys and nervous central system (Ref.10).

Recently, it has been found that endogenous **T_3S** levels in serum are quite high during intrauterine life and as such are kept by the body, i.e. higher than the ones normally found in the adult being, at least until the forth month of postnatal life (Ref.11). Considering the essential role played by thyroid hormones during growth, in particular as far as nervous central system functions are involved, suppositions have been made about the possibility that, in this tissue, **T_3S** may also possibly be used by the body as an occasional source of **T_3**, if and when needed, during the first period of life. Studies performed on autoptic specimens of human nervous cerebral tissue post-mortem showed that the amount of **T_3** in the same results limited by **type III MD** (Ref.12). While this enzyme does not attack **T_3S**, it has been surmised that **T_3S** may exceptionally represent an alternative endogenous source of **T_3** hormone in those tissues which contain sulfatases able to reconvert **T_3S** into its active form, just in case a particular need of the hormone arises in said tissues (Ref's.8, 13).

Further studies have been performed to ascertain the effective role played by **T_3S** during production and metabolism of thyroid hormones. Said studies have recently demonstrated that it shows thyromimetic effects in hypothyroid rats (Ref.10) as well as in euthyroid rats (Ref.14). In both cases **T_3S** has shown a potency of around one fifth that of **T_3**. Moreover both treatments with **T_3S** and with **T_3** produced a significant reduction of serum levels of thyreotropic hormone (**TSH**) in euthyroid rats, thus showing to possess similar capability in inhibiting its secretion. On the contrary, in the case of hypothyroid rats, **T_3S** showed a poor capability of inhibiting **TSH** secretion when compared to **T_3**. It is well known that **TSH** is a highly responsive indicator to the functional status of thyroid gland

and consents to detect the smallest alterations of its hormonal secretion. Actually, its levels are higher under conditions of reduced thyroid functionality, even in those conditions that are defined as sub-clinical, while they are reduced when an excess of thyroid hormones are present. Accordingly, T_3S seems unexpectedly non-comparable to T_3 as far as its capability of inhibition on formation of **TSH** is involved.

In conclusion, particularly in view of the latest studies, a clear and complete knowledge of the biological role played by T_3S has not yet been reached.

In fact its main, well-grounded and universally accepted, feature is its non-biological activity, i.e. it is a biologically inert metabolite of T_3 (Ref's.2 and 3), and the sulfation pathway is regarded as a metabolic activator of T_3 catabolism (Ref.5).

On the other hand, only in particular tissues and under exceptional critical conditions due to shortage of thyroid hormone in those tissues, it has been shown its potential as an endogenous local source of T_3.

As a result, today the skilled technician is still facing a complex, somewhat conflicting, situation, which highlights only some of the biological characteristics of the product and needs more exhaustive in depth studies.

In any case, none of the several documents forming the state-of-the-art discloses, shows or suggests the possibility of using this anomalous metabolite of T_3 in therapy. No close prior-art document, either of experimental nature or substantially speculative, either taken alone or in combination with other related documents, suggests the use, or even the potential use of T_3S as a medicament, taken as such or

preferably in combination with other thyroid hormones or pro-hormones, like, for example T_4. The fact that, only in some specific tissues of the body and under particular, peculiar circumstances, part of T_3S can be reconverted into T_3 does not mean, nor implies, nor suggests that it is possible to generalize this feature to the whole organism through exogenous administration of the product. In particular, there is no suggestion that oral administration of the product, even in protected form according to known methods of the pharmaceutical technique, may render it bioavailable also because it is well known that in those districts where suitable sulfatases are not present the same is rapidly metabolized and excreted through the bile and urines.

SUMMARY OF THE INVENTION

It has now unexpectedly been found, and this is one of the aspects of the present invention, that T_3S, as such or in association with other thyroid hormones or pro-hormones, preferably T_4, and properly formulated according to the desired application, is particularly useful as a medicament to be used in all those pathologies caused by insufficient production by the body of the needed quantities of active thyroid hormones, in particular T_3.

DETAILED DESCRIPTION OF THE INVENTION

In fact, it has unexpectedly been found that the administration of T_3S, contrary to what known about its normal metabolism, allows to maintain steady levels of T_3 in the body for long times (from 12 to 18 hrs) and that results particularly useful in those cases in which it is needed to supplement thyroid hormone in its most active form.

Particularly preferred in the therapy of hypothyroidism, and this is a main aspects of the present invention, is resulted the association of T_3S with T_4. The hormonal association which, in theory, should more accurately mime the normal thyroid secretion is represented by a combination of T_4 with T_3. Actually, pharmaceutical compositions comprising both of said iodothyronines, formulated in proportions similar to the ones of the normal physiologic secretion, have already been tried and marketed. Unfortunately, the oral simultaneous administration of T_4 with T_3 was not able to reproduce the normal thyroid hormones serum levels, because of pharmacokinetics of T_3. In fact, T_3 undergoes a very quick absorption and an equally quick elimination after oral administration; its elimination rate is about 20 times higher than the one of T_4. For this reason administration of T_3 gives raise to a dangerous peak excess in hormone concentration, if compared to the normal physiologic levels, followed by a too much fast drop to sub-physiologic levels. On consequence, today most of the specialised physicians prefer using T_4 alone, even if in this way production of T_3 only depends on the periferic deiodination of T_4, because direct secretion of T_3 by thyroid does not exists or is seriously insufficient.

On the contrary, the association of the invention avoids the above problems, because it has unexpectedly been found that, for example, after oral administration, T_3S provides T_3 serum levels that increase in a gradual way and keep steady for long periods of time, thus preventing the formation of too much high peaks.

Another unespected advantage deriving from the use of T_3S in the treatment of pathologies due to organic deficiency of T_3 consists in its recently found systemic thyromimetic activity linked to a poor inhibition of